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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/518,763	03/03/00	BLISSARD G	BTI-44

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HM12/0412

EXAMINER	
GUZO,D	
ART UNIT	PAPER NUMBER
1636	7

DATE MAILED: 04/12/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/518,763	BLISSARD ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,17,19,2-34, and 36-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-17,19,26-34,and 36-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☒ Other: *detailed action* .

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1-4, 6-7, 9-14, 16-17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cartier et al. in view of Mastrangelo et al.

Applicants claim an insect cell line (i.e. SF21) stably transfected with a first recombinant DNA expression vector comprising a DNA encoding a suppressor of apoptosis, such as the AcNPV p35 gene (and optionally a second recombinant DNA expression vector encoding a selectable marker), such that said cell expresses said suppressor of apoptosis and is resistant to an inducer of apoptosis and a recombinant DNA expression vector encoding a suppressor of apoptosis. Applicants also recite the limitation that the aforementioned cell line, when infected with a vector

expressing a recombinant protein expresses the recombinant protein at higher levels than that of the parental cell line, from which said cell line comprising said suppressor of apoptosis is derived.

Cartier et al. (See whole article, particularly the Abstract, Fig. 1, pp. 7730-7731) teaches a stably transfected insect cell line (derived from SF21 cells) wherein the cells comprise a first recombinant DNA expression vector that encodes (and expresses) the AcNPV p35 gene and a second recombinant DNA expression vector which expresses a heterologous protein (i.e. *neo*) which can be a selectable marker and wherein the stable transfected cell line is resistant to an inducer of apoptosis. Cartier et al. does not recite the production of higher levels of recombinant proteins (compared with parental cells of the cell line) in said cells when said cells are infected with another recombinant expression vector encoding said recombinant protein.

Mastrangelo et al. (Cited by applicants, see whole article, particularly p. 200, right column and p. 201) teaches that co-transfection of cells (including insect cells) with a gene encoding a suppressor of apoptosis and a heterologous gene of interest yields greater production of the heterologous gene product of interest. This is believed to be due to the increased life span of the cells expressing the introduced gene encoding the suppressor of apoptosis.

The ordinary skilled artisan, seeking to generate a cell line stably transfected with a DNA expression vector containing a gene encoding a suppressor of apoptosis and which exhibits increased expression of a recombinant protein of choice introduced into said cell by another expression vector would have been motivated to combine the teachings of Cartier et al. on the generation of insect cells stably transfected with the AcNPV p35 gene combined with the

teachings of Mastrangelo et al. on the use of cells transfected with genes encoding suppressors of apoptosis to express elevated levels of heterologous genes of interest co-expressed with the suppressor of apoptosis gene. It would have been obvious for the ordinary skilled artisan to do this because Mastrangelo et al. specifically teaches that recombinant insect cells which co-express a suppressor of apoptosis and an introduced recombinant heterologous gene of interest express the gene product of interest at higher levels than cells containing the recombinant heterologous gene alone. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rabizadeh et al. In view of Mastrangelo et al.

Applicants claim a cell line stably transfected with a recombinant DNA expression vector comprising a suppressor of apoptosis, wherein the suppressor of apoptosis is expressed and wherein the cell line is resistant to nutrient stress. The cell line is also transfected with a vector encoding a protein of interest wherein the cell line produces the protein at levels higher than that of the parental cell line from which the stably transfected cells were derived.

Rabizadeh et al. (Cited in the previous Office Action, see whole article, particularly the Abstract and p. 2320 and Fig. 4) recites a mammalian neural cell line stably transfected with a recombinant DNA expression vector which expresses the AcNPV p35 gene product and wherein the cell line is rendered resistant to nutrient stress. Rabizadeh et al. does not teach the

transfection of the cells with a expression vector which expresses a recombinant protein at levels higher than in cells from which the stably transfected cell line was derived.

Mastrangelo et al. is cited as in the above 35 USC 103(a) rejection of claims 1-4, 6-7, 9-14, 16-17 and 19-25.

The ordinary skilled artisan, seeking to develop a cell line which could express recombinant proteins at high levels would have been motivated to combine the teachings of Rabizadeh et al. on the ability of a apoptosis suppressor gene to inhibit cell death as a result of nutrient stress with the teachings of Mastrangelo et al. on the ability of cells transfected with a suppressor of apoptosis gene to produce higher levels of recombinant proteins encoded by expression vectors because, as noted by Mastrangelo et al., the increased levels of protein production appear to be due to the longer life span of the transfected cells. It would have been obvious for the ordinary skilled artisan to do this because Mastrangelo et al. notes that the extended life span of cells transfected with a suppressor of apoptosis gene (as disclosed by Rabizadeh et al.) appears to result in higher levels of recombinant protein production in the cells. Given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

3. Claims 26, 30, 32, 33 and 39-40 are rejected under 35 U.S.C. 102(b) as being anticipated by McLachlin et al. (Cited by applicants) in view of Mastrangelo et al. (Cited by applicants)

Applicants and McLachlin et al. recite a method for developing a cell line containing a suppressor of apoptosis (i.e. the Op-IAP) comprising isolating a DNA that encodes a suppressor of apoptosis, constructing a DNA expression vector such that said vector is capable of expressing the suppressor of apoptosis, delivering the vector to a host cell, exposing the cell to an inducer of apoptosis (i.e. actinomycin-D) and selecting cells which survive exposure to the inducer of apoptosis. McLachlin et al. teach co-expression of two genes, a marker gene and a suppressor of apoptosis gene. The two genes are used in selection of cells co-expressing said genes or each gene separately. McLachlin et al. does not teach cells infected with a vector encoding a recombinant protein wherein the protein is expressed at higher levels in the infected cells than in parental cells from which said infected cells were derived.

Mastrangelo et al. is cited as in the above 35 USC 103(a) rejection of claims 1-4, 6-7, 9-14, 16-17 and 19-25.

The ordinary skilled artisan, seeking to generate a method of developing recombinant cell lines containing a suppressor of apoptosis would have been motivated to combine the teachings of McLachlin et al. concerning the generation and selection of cell lines stably transfected with a suppressor of apoptosis gene with the teachings of Mastrangelo et al. on the use of cell lines transfected with suppressor of apoptosis genes to produce high levels of recombinant proteins expressed from recombinant expression vectors in said cells in order to develop cell lines comprising a suppressor of apoptosis gene and a vector encoding a recombinant protein of interest so as to produce higher levels of the recombinant protein of interest. It would have been obvious for the ordinary skilled artisan to do this because Mastrangelo et al. specifically teaches

that cells transfected with a gene encoding a suppressor of apoptosis and containing a expression vector capable of expressing a protein of interest produce higher levels of the protein of interest. With regard to the introduction of the selectable marker on a separate vector, it must be considered that, absent evidence to the contrary, the presence of the selection marker on the same vector or on a different vector would still provide for expression of the selectable marker and would be functionally indistinguishable. Given the teachings of the cited prior art and the level of skill of the ordinary skilled artisan at the tine the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, 4-7, 9-17, 19, 26-34 and 36-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims read on a genus of cell lines (or insect cell lines) from any source stably transfected with any gene encoding any suppressor of apoptosis (or specifically the p35 gene) and

wherein the cells express recombinant proteins at higher levels than parental cells from which the transfected cells were derived, a genus of expression vectors encoding suppressors of apoptosis from any source and a genus of methods employing said suppressors of apoptosis and cell lines containing said genes. Applicants present only examples of Sf9 insect cells stably transformed with the AcNPV p35 gene, expression vectors containing this gene and a method of developing Sf9 cell lines stably transfected with the AcNPV p35 gene.

Since the instant claims read on genus of cell lines stably transfected with genes encoding suppressors of apoptosis, it must be determined if the one example of Sf9 cells is sufficiently representative of the claimed genus. The claims read on hundreds or thousands of different, distinct, cell lines containing any gene encoding any suppressor of apoptosis. The genes encoding suppressors of apoptosis are quite divergent in sequence and biological activity and the elucidation of one such gene would provide little or no information as to whether that gene could be used to stably transform a cell from any given vertebrate or invertebrate species. Likewise, the elucidation of one insect cell line stably transfected with one suppressor of apoptosis gene would not be representative of the hundreds or thousands of different stably transfected cell lines encompassed by the instant claims. Applicants recite DNA expression vectors wherein said vectors encode any suppressor of apoptosis. The claims read on DNA sequences encoding any gene or gene sequence involved in suppression of apoptosis. The claims read on the cDNAs or genomic sequences encoding suppressors of apoptosis. Applicants have presented no written description of any gene encoding any suppressor of apoptosis other than the AcNPV p35 gene. With the exception of the instant examples of DNA expression vectors comprising the p35 gene,

applicants provide no written description of any DNA expression vector which would be able to stably transform any cell. Given the diversity of genes encoding suppressors of apoptosis and the diverse reactions of cells to the recombinant expression of said genes (See for example, Rothe et al., Cell, Vol. 83, 1995, pp. 1243-1252; Seshagiri et al., Current Biology, 1997, pp. 455-460; Miller, J. Cell. Physiol. Vol. 173, 1997, pp. 178-182, etc.), it must be considered that the elucidation of one gene in one expression vector suitable for transforming one insect cell line is insufficient to provide an adequate written description of the claimed genus.

For the written description requirement to be satisfied for a claimed genus a representative number of species must be described by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical or chemical properties by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics sufficient to show that applicant was in possession of the claimed genus. In the instant case, the description of a single example of a cell line stably transformed with a single suppressor of apoptosis gene does not provide sufficient identifying characteristics of the other members of the claimed genus. Likewise, the DNA expression vector comprising the AcNPV p35 gene and methods of making Sf9 cells stably transformed with the AcNPV p35 gene are not sufficient to convince the skilled artisan that applicants were in possession of the claimed genus.

It must be concluded that applicants therefore only provide an adequate written description of insect cell lines stably transfected with the AcNPV p35 gene, recombinant DNA expression vectors encoding the AcNPV p35 gene and methods of developing insect cell lines containing the

AcNPV p35 gene.

Applicants traverse this rejection by asserting that applicants describe several different cell lines in which the instant teachings can be applied and that baculoviruses and suppressors of apoptosis are well known in the art. Applicants also assert that the general rule on adequacy of support is that disclosure of a single species provides support for a generic claim.

Applicant's arguments filed 1/25/01 have been fully considered but they are not persuasive. With regard to applicants disclosure of different cell lines in which the teachings of the claimed invention can be applied, it is noted that applicants merely list several different cell lines and provide no disclosure on stably transfecting these cells with any given suppressor of apoptosis gene so that the cells will produce higher levels of recombinant proteins. With regard to a single species providing support for a generic claim, applicants are requested to review the Guidelines for Examination of Patent Applications under 35 USC 112, 1st paragraph, "Written Description". The examiner has, in the previous Office Action, provided an analysis of the claims using the Guidelines as a guide for determining whether the instant disclosure provides support for the generic claims. Given this analysis, it must be assumed that the skilled artisan would not conclude that applicants were in possession of the claimed genera.

7. Claims 1-2, 4-7, 9-17, 19, 26-34 and 36-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for insect cell lines stable transfected with the AcNPV p35 gene, expression vectors encoding said p35 gene and methods of making insect cells stable transfected with the AcNPV p35 gene, does not reasonably provide enablement

for any cell or insect cell stably transfected with any gene encoding any suppressor of apoptosis, any DNA expression vector encoding any gene encoding any suppressor of apoptosis and a method of making any cell line stably transfected with a gene encoding a suppressor of apoptosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with what is known in the art without undue experimentation (*United States v. Telectronics, Inc.* 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were set forth by the courts in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

1) Unpredictability of the prior art. The art in this area is unpredictable. The generation of cell lines stably transfected with a gene encoding a suppressor of apoptosis such that the cell line is resistant to inducers of apoptosis appears to be a matter of trial and error experimentation. The prior art reveals that apoptotic pathways in many cell or tissue types from different organisms are complex and involves numerous genes that regulate the induction of apoptosis. In order to develop a cell lines stably transfected with a gene encoding a suppressor of apoptosis and capable of expressing the gene product so as to render the cell resistant to inducers of apoptosis, the skilled artisan would need to identify a gene encoding a suppressor of apoptosis in a cell from a

given organism, conduct extensive unpredictable research to determine the apoptotic pathways involved in the cells from which the gene encoding the suppressor of apoptosis gene was isolated, determine how the gene encoding the suppressor of apoptosis functions in the apoptotic pathway in that cell type, determine if other genes are required for the suppressor of apoptosis gene to be effective in suppressing apoptosis in the recipient cell and attempt to develop a DNA expression vector suitable for the cell type which is to be transfected and which will deliver to, stably transfect and express the gene in the target cell in a manner sufficient to render the cell resistant to inducers of apoptosis. All of these steps are fraught with unpredictability.

2) State of the art. The prior art in this area is limited with the few examples the results of apparent trial and error experimentation.

3) Number of working examples. Applicants present working examples involving only Sf9 cells stably transfected with the AcNPV p35 gene, expression vectors comprising the AcNPV p35 gene and methods of making Sf9 cells stably transfected with the p35 gene.

4) Scope of the invention. The claims are broad with the broadest claims reading on any cell line from any source transfected with any gene encoding a suppressor of apoptosis while other claims read on DNA expression vectors containing any gene encoding any suppressor of apoptosis and other claims reading on any cell stably transfected with the p35 gene, etc.

5) Amount of guidance provided by applicants. Applicants provide no guidance on how the skilled artisan would practice the claimed invention using any cell line other than Sf9 and any gene encoding any suppressor of apoptosis other than AcNPV p35.

6) Nature of the invention. The invention involves the complex art areas of identifying the genes

involved in suppression of apoptosis in cells from vertebrates and invertebrates, developing stably transfected cells from invertebrate and vertebrate sources, etc.

7) Level of skill in the art. The level of skill in the art is high; however, given the lack of guidance provided in the instant specification and the broad scope of the claims, the skilled artisan would be left to practice essentially trial and error experimentation in order to reduce to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are essential in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

Applicants traverse this rejection by asserting the same arguments and citing the same case law used to traverse the above Written Description rejection. Since this rejection is made under the Enablement requirement of 35 USC 112, 1st paragraph, arguments directed against a written description rejection are not germane to the rejection at hand.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-38 and 43-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37 and 43 recite a "baculovirus expression system". It is unclear if these claims are

intended to be a composition claims or method claims because the claims contain components which are parts of a composition and also these claims recite method steps for using the compositions. Applicants need to redraft the claims to more adequately define what is being claimed, i.e. a baculovirus expression system which is a composition or a baculovirus expression system which is a system for expressing proteins of interest.

Claim 44 is vague in that applicants recite exposing the cells to an inducer of apoptosis in step d) and then recite in step e), the phrase "such that apoptosis induced by a baculovirus infection is inhibited". It is unclear how the baculovirus infection of step e) relates to the inducer of apoptosis recited in step d), i.e. are these inducers of apoptosis the same? Is the baculovirus infection recited in step e) the same as the inducer of apoptosis recited in step d)?

In view of the new rejections (necessitated by applicants' amendments) based upon the prior art, applicants' arguments directed to the withdrawn rejections are moot.

No Claims are allowed.

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Robert Schwartzman, can be reached on (703) 308-7307. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding or relating to attachments to this Office Action should be directed to Patent Analyst Zeta Adams whose telephone number is (703) 305-3291.

David Guzo
April 9, 2001

DAVID GUZO
PRIMARY EXAMINER
David Guzo